Remarks

Claim amendments

Claims 21, 22, 25, and 27 are amended to attend to matters of form. Support for the amendments is found in at least the original claims and Examples 1–3 (pages 28-38). No new matter is added by these amendments.

Enablement of claims 1, 3–8, 10–12, and 14–16

Claims 1, 3–8, 10–12, and 14–16 have been rejected for allegedly lacking enablement commensurate with their full scope. The Examiner has stated that the claims are enabled for use with a fetal-derived cell but not with an adult-derived cell. This allegation is based on an interpretation of literature references and the alleged "absen[ce of] evidence to the contrary." However, this rejection overlooks working examples disclosed in the present specification, and moreover, is based on misapprehension of reference disclosure and application of an improper legal standard. Applicants respectfully request reconsideration and withdrawal of the rejection for at least these reasons, which are set forth in greater detail below:

A. The rejection overlooks working examples disclosed in the present specification.

The specification discloses working examples in which **adult cells** were successfully treated with an embodiment of the claimed method. Five adult-derived cells gave rise to blastocysts by nuclear transfer, which were then implanted into a host animal (specification, pages 37-38). Fibroblasts derived therefrom had greatly extended lifespan. Table 1 (specification, page 38; reproduced in part below) shows that prior to this treatment, the adult cell populations had 4 or fewer population doublings remaining, but after treatment, the resulting cells had about 85.86 to 91.44 population doublings remaining.

Table 1. Population doublings in fibroblasts derived from normal fetuses and fetuses generated from clonal populations of adult senescent cells

Cloned Fetus	PDs left at time of nuclear transfer in original adult cells	PDs in fibroblasts isolated from the fetus
25-1	0.26	90.14
25-2	0.0	91.44
14-1	4.0	89.27
14-2	1.0	90.34
22-1	2.5	85.86

In the right-most column of Table 1, "isolated from the fetus" refers to adult-derived cells after being treated by an embodiment of the claimed method and isolated from a fetus. PDs: Population doublings. (The omitted portion of the table shows results for fibroblasts derived from normal fetuses.)

Thus, contrary to the alleged basis of rejection, the specification does provide working examples using adult-derived cells, and does contain ample evidence that directly refutes the Examiner's allegation that the claims would not be enabled for adult-derived cells.

B. <u>The rejection relies on mischaracterization of reference disclosure.</u>

The purported evidence that the claimed methods would be inoperative with adult-derived cells is the shortened telomeres of "Dolly," which was cloned from cultured adult cells. Specifically, Shiels *et al.*[1] reports that Dolly had shortened telomeres relative to non-cloned control sheep of the same age. The Examiner further cites a post-filing publication, Lanza *et al.* Science 288:665-9 (2000), which stands in apparent contrast to the Shiels *et al.* results. Lanza *et al.* reports that cloned cattle had elongated telomeres relative to non-cloned control cattle of the

[1] Though not cited in the Office Action, the statements regarding Dolly's telomeres are understood to refer to Shiels *et al.*, "Analysis of telomere length in Dolly, a sheep derived by nuclear transfer," Cloning 1999;1(2):119-25.

same age. Lanza *et al.* provide several possible explanations for the differences between their results and the Shiels *et al.*, one of which was "differences in. . . donor cell types." Lanza *et al.*, page 668, third column. The Examiner further cites Ulaner *et al.* for the proposition that fetal fibroblasts express telomerase (as discussed below, this statement mischaracterizes the reference disclosure). From these results, the Examiner concludes from these results that "the art taught only lengthening of telomeres and otherwise 'rejuvenation' of the cells occurred only when nearly senescent fetal fibroblasts were used." This attribution of telomere shortening of cloned organisms to the telomerase status of donor cells appears to be based solely on the Examiner's conjecture, as the cited references include no such statement.

Contrary to the Examiner's assertion, Ulaner *et al.* does not disclose that fetal fibroblasts express telomerase. Indeed, Ulaner *et al.* does not even include the word "fibroblast," except in the titles of two cited references. Rather, Ulaner *et al.* only reports telomerase assays of homogenized whole organs (lung, liver, spleen, testis, heart, brain, and kidney) at different times during fetal development. Each of these organs are comprised of multiple cell types, and thus the reported whole-organ experiments do not permit determination of which cell type(s) might express telomerase activity. Ulaner *et al.* reports that telomerase activity is detectable in each of these organs at eight weeks, but disappears from some of these organs before 21 weeks (Fig. 1). Ulaner *et al.* further shows that telomerase activity correlates with the presence of precursor cells, suggesting that precursor cells—and not differentiated cells such as fibroblasts—are likely responsible for the observed telomerase activity (see paragraph spanning pages 771–772). From these results, the reference concludes that:

> The correlation of telomerase activity in fetal tissues with the histological presence of tissue specific precursor stem cells lends support to the hypothesis that **undifferentiated stem cells are responsible for telomerase activity in the human fetus**.

Ulaner *et al. et al.*, pg. 773 (emphasis added). Thus, in contrast to the Examiner's characterization, Ulaner *et al.* does not teach that fetal fibroblasts express telomerase; rather, Ulaner *et al.* suggest that precursor cells are responsible for the observed telomerase activity. Accordingly, the Examiner's conjecture is unsupported by Ulaner *et al.* and thus fails to account

for the apparent discrepancy between the Shiels *et al.* and Lanza *et al.* results, and accordingly the reference does not support the alleged basis of rejection.

C. <u>The rejection employs an improper legal standard.</u>

The Examiner has alleged that the claims are non-enabled for encompassing both operative and inoperative embodiments. Even if this allegation were true (which Applicants vigorously dispute above), this alone would not support an enablement rejection. The proper inquiry is set forth below:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative **<u>with expenditure of no more effort than is normally required in the art</u>**. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling).

MPEP 8th ed., rev. 6, § 2164.08(b) (emphasis added). Under the proper standard, an enablement rejection would only be justified if abnormal levels of effort were required to determine which embodiments were operative. The Examiner has made no such allegation. Rather, in light of the disclosed working examples, the person having ordinary skill in the art would readily be able to perform the recited steps on a given cell type and determine whether "a cell of the same type as the mammalian primary cell, wherein the remaining number of population doublings of the isolated cell is greater than the remaining number of population doublings of said mammalian primary cell" had been obtained. Accordingly, testing to identify operative embodiments would require no abnormal degree of effort, and the mere existence of inoperative embodiments (if any) would not justify the present rejection under the proper legal standard.

Enablement of claims 7, 14, 21–25, 27-36, and 106

Claims 7, 14, 21–25, 27-36, and 106 have been rejected for allegedly lacking enablement commensurate with their full scope. The Examiner has stated that part of the claim scope is enabled, but has alleged that the claims are not enabled to the extent that they include: 1) performing homologous recombination using near-senescent cells; 2) developing a mammal by transferring an ES cell alone into a female host; or 3) genetic modification in any culture of donor cells other than a fibroblast. The only claims specifically mentioned in the rejection are claims 7 and 25, and it is unclear precisely how these rejections may have been intended to be applied to the other listed claims, or if some or all of the claims besides 7 and 25 may have been included in error. To the extent that the alleged basis of rejection may be though to apply to the remaining claims, applicants respectfully submit that those claims are enabled for at least the reasons described below with reference to claims 7 and 25. If the rejection is maintained as to any of the other listed claims, applicants respectfully request that the Examiner particularly relate each alleged basis of rejection to such claims so that applicants may have a full and fair opportunity to respond.

The Examiner has alleged that in claims 7 and 25, "Genetic modification encompasses homologous recombination. . . . The claims **require** doing so in a senescent or near senescent cell." This position misapprehends how the claims would be understood by one of skill in the art when read in light of the specification. Claim 7 recites that "prior to step (a)" a genetic alteration is performed. Similarly, claim 25 recites "providing a primary mammalian cell that has been genetically altered." These claims would properly be understood to encompass genetic alteration of the cell's progenitor. Thus, neither claim requires that the cell be senescent or near senescent at the time of genetic alteration. One of ordinary skill in the art can readily ascertain whether a cell has sufficient proliferative capacity remaining for use in a given method of genetically modifying a cell. For example, microinjection of a desired construct could be performed concurrently with nuclear transfer, in which instance no further proliferative capacity would be needed. Accordingly, it would be unduly limiting to require further limiting the claims to a particular degree of remaining proliferative capacity.

Moreover, the alleged basis of rejection inappropriately focuses on only one particular form of genetic modification, namely homologous recombination. Neither claim is so limited.

Rather, Claim 7 recites "said mammalian primary cell is transfected with at least one heterologous gene or at least one native gene of said mammalian primary cell is disrupted" and claim 25 recites "providing a primary mammalian cell that has been genetically altered." Even if some possible embodiments may be thought to be inoperative (e.g., homologous recombination may be difficult to achieve in fully senescent cells) it does not render the claim non-enabled; rather, as discussed above, **the proper test is "whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art.**" MPEP 8th ed., rev. 6, § 2164.08(b) (*citing Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)) (emphasis added). If indeed the references convincingly teach inoperability of any particular embodiments (which applicants dispute) such teachings would only reinforce the notion that operative and inoperative embodiments can be identified with no more effort than normally required in the art; accordingly would only further support enablement of the present claims under the proper legal standard. For example, one of ordinary skill in the art can readily determine which methods of genetic alteration can be used with a given source of cells, e.g., by measuring the proliferative capacity of a the given cells and comparing to the number of population doublings required to practice a given method of genetic modification. These types of measurements are exemplified in Denning *et al.* (cited by examiner) which concludes that about 45 population doublings were required to practice a particular protocol, and shows that some cells had sufficient proliferative capacity for this protocol but others did not. Thus, at most, Denning *et al.* demonstrates that a particular desired embodiment can be routinely tested to determine operability, indicating that the claims are enabled.

Moreover, the Denning *et al.* protocol included steps not required in the present claims, such as growing sufficient cells for cryopreservation before and after genetic modification, growing sufficient numbers of cells for electroporation, and serum starvation prior to NT (see Clark *et al.*, Figure 3, which illustrates how the estimated 45 population doublings of the Denning *et al* method are expended through the various steps). Denning *et al.* were further encumbered by the belief that senescent or near-senescent cells could not be used for nuclear transfer (which was overcome by the present disclosure). In this regard, rejection states that "the claims are not enabled so far as they require genetic modification in culture that is demonstrated

by the art to drive the cells to a senescent state to the extent that they are no longer effective in completing the nuclear transfer process." Office Action, page 7. However, the present specification provides methods of nuclear transfer that may be performed in senescent or near-senescent cells, overcoming this limitation faced by Denning *et al.* Even if cells are rendered senescent or near-senescent during the course of genetic modification, they nonetheless may be used for nuclear transfer in the presently claimed methods.

Clark *et al.* (2000) (cited by examiner) also does not support the allegation that only fetal fibroblasts could be used for genetic modification, but rather provides further discussion of methods that require less proliferative capacity than those described in Denning *et al.* For example, Clark *et al.* describe that direct nuclear injection and other delivery systems can achieve greater efficiency than electroporation, indicating that technical challenges encountered by Denning *et al.* can be readily overcome. Accordingly, even if some cell types could not be used in the method of Denning *et al.* these cell types nonetheless could be used in the present methods, for example by omitting steps which unnecessarily consume population doublings; using methods with improved efficiency of gene introduction; and using senescent or near-senescent cells for nuclear transfer.

The Office Action further cites Cibelli *et al.* (1998) and Schnieke *et al.* (1997) for the proposition that "only fetal fibroblasts had been genetically modified at all." Office Action, page 6. These references show successful use of fetal fibroblasts for genetic modification followed by nuclear transfer. However, neither reference reports any attempt to use any other type of cells. These literature reports on one type of cell do not demonstrate inoperability of other types of cells.

As to the allegation that claim 25 "require[s] generating a newborn mammal using a naked ES that has not been introduced into a blastocyst" the claim recited "introducing said . . . embryonic stem cell into a recipient mammalian female" but did not require that the ES cell alone would be introduced; rather, one of ordinary skill in the art would readily understand that an ES cell could be contained in a blastocyst (e.g., a diploid or tetraploid blastocyst) to give rise to an animal. Nonetheless, to advance the prosecution of the application, claim 25 is amended to recite "allowing said embryo or **a blastocyst containing said** embryonic stem cell to fully

develop such that said female delivers a newborn animal having the same genotype as the cell resulting from step (a) **or a chimeric newborn animal containing cells of the same genotype as the cell resulting from step (a)**" rendering the alleged basis of rejection moot. (Though not specifically identified in the rejection, claim 27 is similarly amended, rendering the alleged basis of rejection inapplicable to this claim as well.)

Definiteness of claims 7, 14, 21, 22, 25 and 106

Claims 7, 14, 25, and 106 have been rejected as allegedly indefinite. The rejection of claim 25 refers to recitations that are not included in claim 25 but instead were present in claims 21 and 22; accordingly, these claims are also addressed here.

Claims 7, 14, and 106 were rejected as allegedly vague for not being clear whether a genetic alteration "is intended to occur using recombinant methods or if a randomly occurring mutation or other genetic alteration is intended." However, this is an improper basis of rejection because "**[b]readth of a claim is not to be equated with indefiniteness**." MPEP 8th ed., rev. 6, § 2173.04 (*citing In re* Miller, 441 F.2d 689, 169 USPQ 597 (CCPA 1971)) (emphasis added). Rather, the proper inquiry for determining definiteness is set forth as follows:

> The essential inquiry pertaining to [the definiteness] requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
>
> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art; and
>
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

MPEP 8th ed., rev. 6, § 2173.02. Thus, the relevant inquiry for determining definiteness of a claim is not the breadth of that claim. Claims 7, 14, and 106 particularly point out and distinctly

claims subject matter which the applicant regards as the invention. There is no ambiguity as to their scope. One of skill in the art will readily understand that the claims include (without limitation thereto) recombinant methods as well as naturally arising mutations which may be identified by screening or selection (one well-known example being negative selection for spontaneous loss of thymidine kinase gene function through growth in the presence of thymidine analogues). Thus, the fact that each of the embodiments described by the Examiner are embraced by the claim does not render that claim indefinite. Rather, in light of the teachings in the specification, high level of skill in the art of genetic modification, and generally well-developed literature concerning methods of genetic modification (including several of the references cited in the Office Action) the subject matter of the claims is sufficiently clear.

Claim 25 was also rejected to for allegedly being unclear what "the cell" refers to in steps (b) and (c) in the claim. It is respectfully submitted that one of skill in the art would readily understand which cell was referred to at each point in the claims. Nonetheless, to advance the prosecution of the application, claim 25 is amended herewith to remove this recitation in step (b), rendering the alleged basis of rejection moot. Step (c) does not recite "the cell" and clarification is respectfully requested whether some additional basis of objection was intended to be stated.

The objection also refers to alleged lack of clarity for the recitation "'the cell resulting from the nuclear transfer' as multiple round of nuclear transfer are encompassed by the claim" which appears to be a rejection of claims 21 and 22 (in which this phrase appears) and not claim 25 (which includes this phrase only in an unambiguous context). As the Examiner notes, the claims encompass methods in which one or multiple nuclear transfer steps are performed. Claims 21 and 22 are amended to recite "wherein the cell resulting from the **first** nuclear transfer has an increased number of possible population doublings remaining as compared to the mammalian primary cell" which clarifies the intended meaning and renders the alleged basis of rejection moot.

The objection refers to the recitation "between genetic manipulations" which is interpreted to be a rejection of claims 21 and 22 (in which this phrase appears) and not claim 25 as stated. The alleged basis of the objection is that "the claim appears to have no beginning step." Office Action, page 8. However, claims can (and often do) encompass performing the recited steps in more than one possible order. *See* MPEP 8th ed., rev. 6, § 2111.01 (*citing Altiris*

Inc. v. Symantec Corp., 318 F.3d 1363, 1371, 65 USPQ2d 1865, 1869-70 (Fed. Cir. 2003) (it was improper to read a specific order of steps into method claims where, as a matter of logic or grammar, the language of the method claims did not impose a specific order on the performance of the method steps, and the specification did not directly or implicitly require a particular order)). Present claims 21 and 22 provide "A method of performing compound genetic manipulations in a mammalian primary cell" and refer to additional steps to be performed "between genetic manipulations." The claims encompass steps of performing genetic manipulations and additional steps to be performed between genetic manipulations. There is no requirement that the claim be limited to a particular "beginning" step. Nonetheless, to advance the prosecution of the application, claims 21 and 22 are amended herein to recite "**performing multiple genetic manipulations of a mammalian primary cell and**, between genetic manipulations. . ." rendering the alleged basis of rejection moot.

CONCLUSION

In view of the foregoing, all claims are believed to be in condition for allowance. In the event that any additional issues remain, or if it would expedite the prosecution of this application, the Examiner is respectfully invited to contact the undersigned (direct line, 703-714-7645).

The Director is hereby authorized to charge any fees (including fees for extensions of time that may be required for consideration of this paper or to maintain the pendency of this application), or credit any overpayments, to our **Deposit Account No. 50-0206.**

Respectfully submitted,
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